EXHIBIT O

Structure-activity relationship in nonsteroidal antiinflammatory agents, including QSAR in fenamate derivatives.

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First, it is shown that it is not yet possible to outline a generally valid receptor model for the non-steroidal anti-inflammatory agents. This is demonstrated by three examples of receptor models, namely by the model according to Shen, by the receptor concept of Appleton and Brown, and by the concept concerning chelate complex formation between NSA and heme iron of the cyclooxygenase complex according to Peterson et al. This means that the "custom-made" synthesis of NSA with, perhaps, quantitatively and qualitatively better properties is not yet possible. On the basis of this statement, QSAR investigations may be justified in order to optimize known NSA. In this paper, QSAR calculations on 21 fenamate derivatives are reported. For this, both the multivariate and the univariate Hansch Analysis were used. Altogether, 16 approaches to QSAR has been performed using 1 - 4 biological and 3 - 19 physico-chemical parameters, respectively, with 7 - 21 objects. In all cases a dominating influence of pi has been indicated. Other physico-chemical parameters seemed to be of less importance, e. g., sigma, Es, log xi MR, MV, parachor, and Verloop's steric constants. Possible new fenamate structures of higher biological activity are briefly discussed.

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STRUCTURE-ACTIVITY RELATIONSHIP IN NONSTEROIDAL ANTIINFLAMMATORY AGENTS, INCLUDING QSAR IN FENAMATE DERIVATIVES

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The present conceptions of the relationship between chemical structure of the nonsteroidal antiinflammatory agents (NSA) on the one hand and of the respective receptor for the anti-inflammatory action on the other hand are still relatively rough and little uniform. This shall be demonstrated by 3 examples:

1. Conceptions of the receptor have been developed using the chemical structure of the most effective NSA, e. g. of indomethacin by Shen (1; Fig. 1). Accordingly, the carbonyl

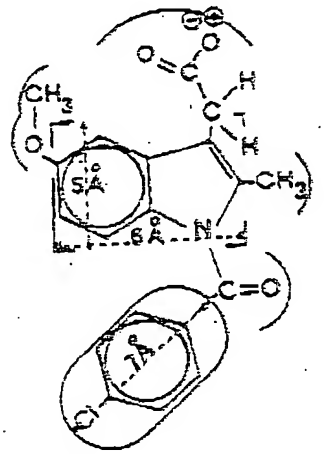
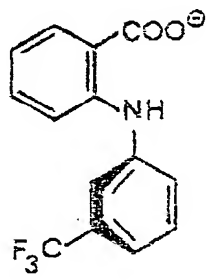
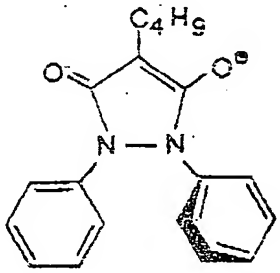


Fig. 1: Receptor model according to the chemical structure of indomethacin (1)

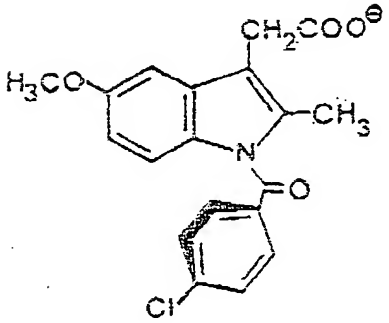
group is bound at an anionic binding site of the receptor, the indol ring and its methyl and methoxy group correspond with a flat area and the respective supplementary binding sites, and the p-chlorobenzoyl moiety is placed in a shallow trough so that the p-chlorobenzoyl moiety is twisted against the indol ring system and in an angular position to it. This torsional and angular position of the second ring holds also true for other acidic NSA (Fig. 2). In diclofenac e. g., the angle



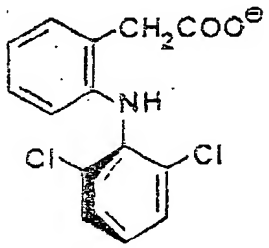
flufenamic acid



phenylbutazone



indomethacin



diclofenac

Fig. 2: Chemical structure of flufenamic acid, phenylbutazone, indomethacin, and diclofenac, resp., showing the torsional and angular position of the aromatic substituent (2)

amounts to 69° (2). Therefore, the conceptions of the receptor are also compatible with these substances. The higher the chemical conformity between NSA and receptor the better the activity of the compound.

At present, the predominant opinion is that the receptor of the acidic NSA is represented by the cyclooxygenase which catalyses the biosynthesis of the prostaglandins. By interference of the acidic NSA with the receptor, the natural substrates of the cyclooxygenase cannot be converted into the prostaglandins and the respective endoperoxides. The most important natural substrate seems to be the arachidonic acid.

Gund and Shen (3, 4), on the basis of X-ray analysis of NSA and of computer estimation of the probable conformation of the substrate arachidonic acid, have recently improved the conceptions of the chemical relationship between structure of NSA and their receptor. According to that (Fig. 3), the anionic binding site is followed by an ample hydrophobic site or pocket, at which upper part the Δ^5 double bond of the arachidonic acid is apparently hydrophobically fixed, only. In its lower part, the Δ^8, Δ^{11}, and Δ^{14} double bonds are bound at three respective electron acceptor regions. The abstraction of hydrogen at C-13 of the arachidonic acid as the initial result of interaction with the receptor takes place from below, the following uptake of oxygen at C-11 occurs from above the plane. Besides indomethacin, the NSA sulindac fits well with this receptor model (4).

However, the fitting of the salicylates, fenamates, and pyrazolidinediones as well as of sudoxicam is rather poor. It seems important to emphasize that in this model the carboxyl group of the natural substrate corresponds to that of the inhibitor.

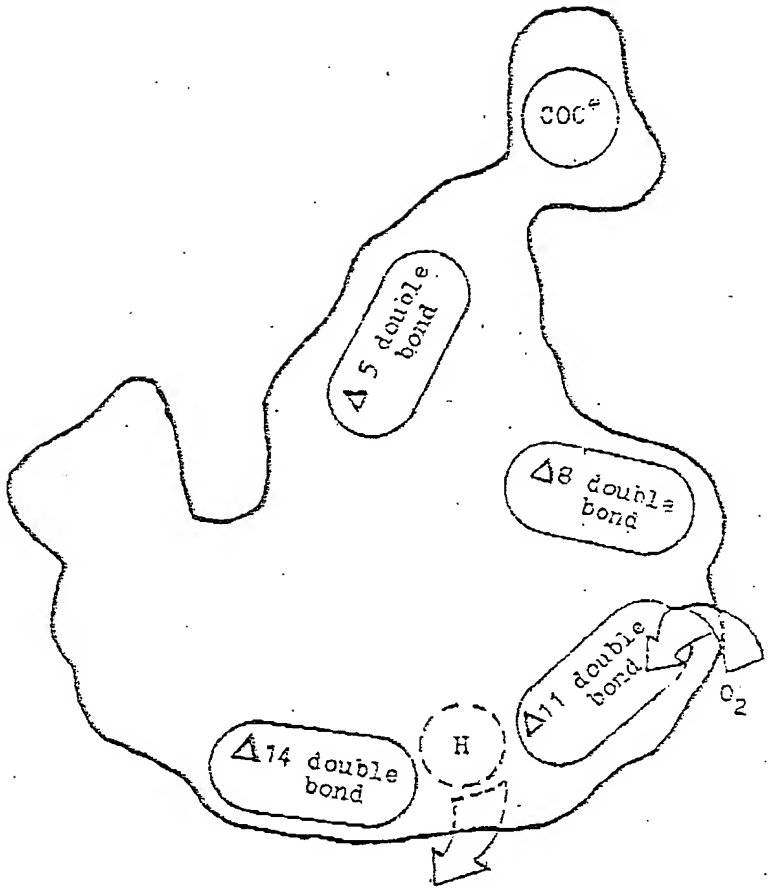


Fig. 3: Receptor site of acidic NSA constructed according to the probable conformation of the substrate arachidonic acid (3, 4; slightly modified)

2. Using space-filling models of the peroxy radical as the precursor of the cyclic endoperoxide of the arachidonic acid, PGG_2, as well as of models of 2(S)-(3-chloro-4-cyclohexylphenyl) propionic acid and other acidic cyclooxygenase inhibitors, Appleton and Brown (5) were able to disclose some common structural features. According to this, the peroxy radical of arachidonic acid (Fig. 4, formula I) in its favoured conformation

Fig. 4: Chemical structure of the peroxy radical of arachidonic acid (I) in its favoured conformation (II) and of the NSA 2(S)-3-chloro-4-cyclohexylphenyl)propionic acid (III) as well as of indomethacin (IV), ketoprofen (V), fenoprofen (VI), alclofenac (VII), ibuprofen (VIII), and naproxen (IX), resp.; (5), modified

immediately prior to its cyclisation (formula II) is most similar to the structure of 2(S)-(3-chloro-4cyclohexylphenyl) propionic acid (formula III) as well as to that of indomethacin (formula IV), ketoprofen (formula V), fenoprofen (formula VI), diclofenac (formula VII), ibuprofen (formula VIII), and naproxen (formula IX), respectively. The similarity mainly applies to the bold lines of the structures. The most striking difference to the conceptions of Shen (1, 3, 4) consists in the fact that the carboxyl group of the NSA now corresponds and, therefore, competes, with the peroxy group in position 11 of the peroxy arachidonic acid. Part of the phenyl-ring of III would occupy a π electron acceptor site of the receptor which is related to the π system of $C_{13} - C_{15}$ of the physiological substrate. The chlorine atom at the phenyl ring has that favourable position of disturbing the function of the peroxy group at position 15 at which oxidation of the fatty acid takes place (formula I). The cyclohexyl ring would occupy an area of the enzyme which normally fits to section $C_{17} - C_{20}$ of chain of the fatty acid. The (S)-methyl substituent lies below the plane of the phenyl ring and would be accomodated by a "groove" in the enzyme which normally accepts the region of C_7 of the physiological substrate.

3. Recently, Peterson et al. (6,7) have again called attention to the chelate complex forming properties of some NSA. They have been able to suggest that indomethacin, ibuprofen, and tolmetin inhibit cyclooxygenase by binding at the cationic binding site which consists of one of the ligands of the iron on one side of the heme of the cyclooxygenase complex and by binding at the hydrophobic region of the heme (Fig. 5). Accordingly, acid NSA do not interact with cyclooxygenase itself but with its heme complement (see 18, 19). In this model, acid NSA do not interfere with the active site of the cyclooxygenase complex which is represented by the second ligand of the iron on the other side of the heme at which the iron bound to oxygen interacts with the double bond at C_{11}, i. e. at the site of

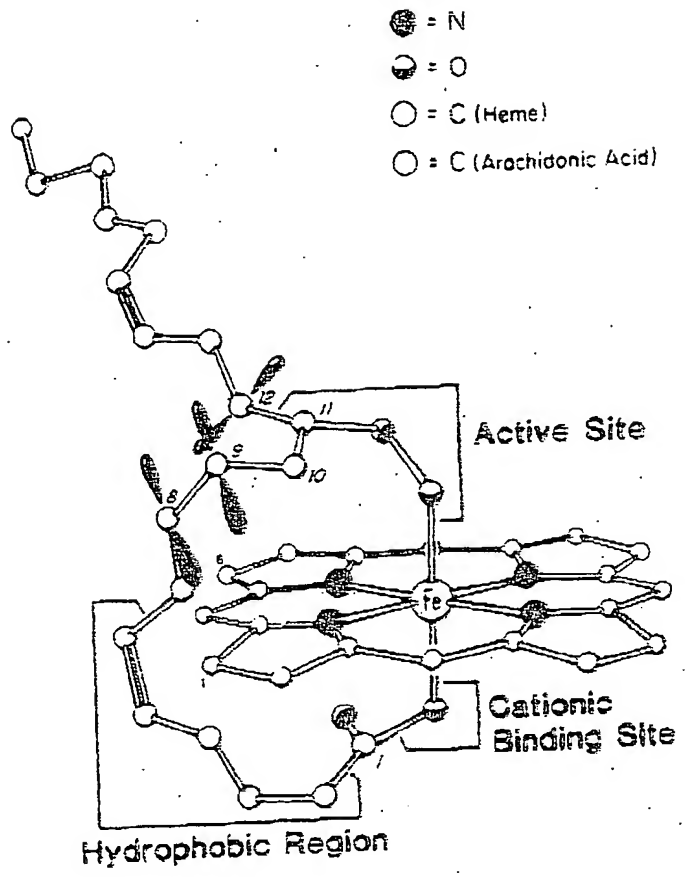


Fig. 5: Interaction of arachidonic acid with heme. Cationic binding site refers to binding of the carboxyl group with Fe^{2+} ligand below the plane of the porphyrin ring. Position 11 of arachidonic is linked to the second ligand of Fe^{2+} above the plane of the heme by the peroxy group forming the peroxy radical.

peroxy radical formation of the arachidonic acid (Fig. 5). This is because, in contrast to arachidonic acid the acidic NSA, are too short and/or too rigid to wind stereochemically round the protoporphyrin ring in order to reach the second ligand site of

the iron. The non-occupation of this second ligand might be the explanation for the inability of indomethacin to inhibit the peroxidase activity of the PG endoperoxide synthetase enzyme (6), and, moreover, the lipoxygenase pathway which does not require the heme complement.

These three examples show that it is not yet possible to outline a generally valid receptor model and that the conceptions of the fine-structure are little uniform. This means that the "custom-made" synthesis of NSA with, perhaps, quantitatively and qualitatively better properties is not yet possible. This may justify our investigations to optimize known NSA by means of QSAR (8 - 12), which can both lead to more effective congeners of NSA and contribute to concepts of the chemical structure of NSA as well as of their receptors. In this paper, it is reported on fenamates.

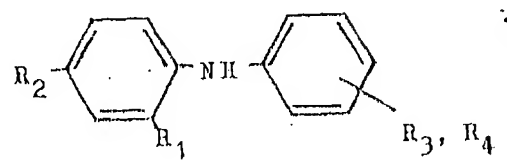
Materials and methods

The fenamic acid derivatives have been synthetized by Hannig et al. (13, 14). Their chemical structure is depicted in Table 1. They were tested in the carrageenin rat paw edema at the dose of 100 mg/kg orally, except diclofenac (Ciba-Geigy AG, Basel) which was tested at the dose of 5 mg/kg. Carrageenin (sub-plantarly 0.1 ml of a 1 % Viscarin solution, Marine Coll. Inc., Springfield) and the test substance were given simultaneously. Inhibition (%) of edema development was measured by comparison with a control group at hour 2, 3, and 4, resp., after carrageenin injection. Usually 10 rats were used per group. Data are taken only as the mean of the respective group.

The physico-chemical parameters of π, E_s, σ, $\log f$, MR, MV, parachor and Verloop's constants are taken from the literature or have been calculated according to the respective instructions.

Table 1: Chemical structure of compounds tested as well as biological activity (edema inhibition in % at hour 2, 3, and 4, resp., after substance administration as well as total activity as the sum of the inhibition values). The physicochemical parameters used and the dose administered are given below.

No	R_1	R_2	R_3	R_4	edema inhibition 2. h	3. h	4. h	sum (Σact.) 2. - 4. h
1	COOH	H	2-CH_3	3-CH_3	50	46	35	131
2	COOH	H	3-CF_3	H	47	62	45	154
3	COOH	H	3-Cl	4-CH_3	55	47	46	148
*4	CH_2COONa	H	2-Cl	6-Cl	50	64	71	185
5	COOH	H	H	2-COOH	12	13	17	42
6	COOH	H	H	3-COOH	15	20	16	51
7	COOH	H	H	4-COOH	10	8	18	36
8	COOH	OCH_3	2-Cl	H	20	11	16	47
9	COOH	OCH_3	3-Cl	H	34	46	33	113
10	COOH	OCH_3	4-Cl	H	10	15	1	26
11	COOH	OCH_3	2-Cl	3-Cl	56	63	61	180
12	COOH	OCH_3	2-Cl	4-Cl	8	24	25	57
*13	COOH	OCH_3	2-Cl	5-Cl	49	40	13	102
14	COOH	OCH_3	3-Cl	4-Cl	44	21	5	70
15	COOH	OCH_3	4-Br	H	21	40	39	100
16	COOH	OCH_3	3-CH_3	H	34	31	28	93
17	COOH	OCH_3	4-CH_3	H	47	27	6	80
18	COOH	OCH_3	2-CH_3	3-CH_3	42	59	46	147
19	COOH	OCH_3	2-OCH_3	H	21	13	14	48
20	COOH	OCH_3	4-OCH_3	H	26	9	19	54
21	COOH	OCH_3	3-CF_3	H	28	51	65	144



π, E_s, σ, logβ, MR, MV, parachor, Verloop's constants

100 mg/kg p. o. (diclofenac 5 mg/kg)

*excluded from some calculations

Results

The edema inhibiting activity of the substances at hour 2, 3, and 4 after carrageenin injection as well as their total activity as the sum of per cent inhibition at hour 2, 3, 4, are listed in Table 1. First, the relationships between physico-chemical constants and biological activity are depicted in simple graphs. In Fig. 6, an example is given of the relationship between π and σ values, respectively, and total activity (in parentheses next to the code of the respective substance).

According to Fig. 6, the total activity (Σ act.) increases with the increase of π in the series of the 3-substituted compounds. The flufenamic acid exhibits as the best compound in this series. Above all, σ does not show any characteristic correlation with the biological activity. The activity of the chlorine derivative decreases if the compound is additionally chloro-substituted in 4-position. The 4-monosubstituted OCH_3 and COOH derivatives show also little antiinflammatory activity. Likewise, mono substitution of the 2-position seems not to be of advantage (see the 2-Cl, 2-OHC_3, and 2-COOH compounds). This could point to an influence of the position of the substitution. However, substitution in both 2- and 4-position is generally not unfavourable in the case of disubstitution, since the 3-chloro-4-methyl derivative and the 2,3-dimethyl derivative (mefenamic acid), respectively, are as effective as the 3-flucromethyl derivative (flufenamic acid). This could be connected with the negative σ-effect of the methyl group in presence of the considerably positive π-effect of the contiguous group. The 2-substitution also implies high effectivity in diclofenac. Altogether, the antiinflammatory activity increases with the further increase of lipophilicity, as is shown by the 2,3-dichloro derivative and by diclofenac.

Starting from the flufenamic acid as one of the best compounds introduced into the market, one can hardly deduce a proposal

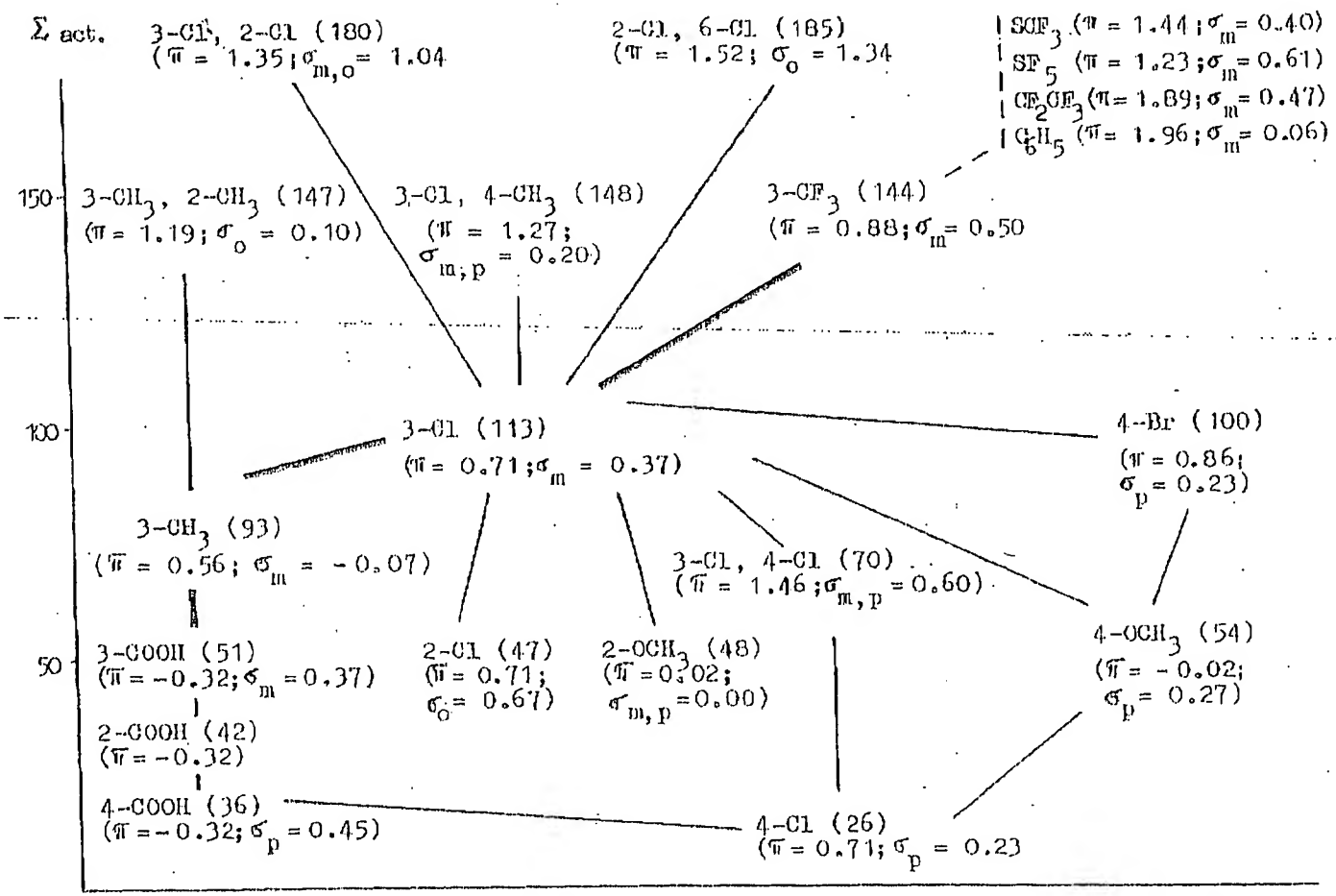


Fig. 6: Relationship between π and σ, resp., and antiinflammatory activity (Σact.) of fenamates

being noteworthy for the synthesis as a new compound which could be expected to be superior to the 2,3-dichloro derivative. While, according to Fig. 6, the SCF_3 and SF_5 substituents do not show essentially better π - and σ-values, the CF_2CF_3 substituent only exhibits better physico-chemical parameters and, therefore, could give expectation of leading to a more active compound than being those which have been tested. As to the possibility of coming to substances of higher effectivity by synthetizing disubstituted compounds it has to be mentioned that the synthesis of this kind of compounds with two electron withdrawing substituents in close vicinity cannot be made without greater trouble (15). Thus, the graph of Fig. 6 results in the conclusion that the optimization in the series of the compounds in question seems practically have come to an end.

In order to more precisely clear up this question, a QSAR has been performed. For this, we used both the multivariate and univariate Hansch Analysis (16 - 17). In this connection the suitability of ξ, being recently introduced as a new physico-chemical parameter in QSAR (9), has also been reinvestigated.

The first problem was the question the π-values of which basic body would fit best with the fenamates. For this, the respective π-values of benzene, phenol, aniline, phenyl acetic acid, and phenoxy acetic acid were included in the QSAR. As can be seen from the correlation matrix (Table 2), the values of phenoxy acetic acid fit best with the biological data. By the way, the coefficients related to phenol, aniline, and phenyl acetic acid (not given in Table 2) were between those related to benzene and phenoxy acetic acid. This could mean that substitutions at an acidic phenyl basic body are more effective than substitutions at the benzene ring. Indeed, the basic structure of fenamates is that of an acidic phenyl basic body. In any case, the π-values of the phenoxy acetic acid are then preferentially used in the QSAR. Possibly, the methoxy group of the anthranilic acid moiety has an absorption inhibiting influence which is

mainly valid during the first hours but is then receding so that the total activity seems not to be reduced. This could be indicated by the negative dummy variable decreasing with time (Table 2).

Table 2: yx correlation matrix of QSAR, concerning π-values of substituents at different basic bodies as well as the dummy variable

y \ x	π_{benz}	π_{phoxac}	π_{phac}	dummy
2 h	0.4152	0.4390	0.3782	-0.4917
3 h	0.5247	0.6206	0.6153	-0.4212
4 h	0.2969	0.3934	0.4262	-0.3156
QU	0.4763	0.5633	0.5548	

Altogether, sixteen approaches to the QSAR has been performed using 1 - 4 biological and 3 - 19 physico-chemical parameters, respectively, with 7 - 21 objects. As had to be expected, the use of a large number of physico-chemical parameters gave relatively high correlation coefficients (up to r = 0.973) but without any statistical significance. However, in all cases a dominating influence of π was indicated which is in line with the results obtained from Fig. 6.

Using the antiinflammatory activity at hour 2 after treatment only, and π, log ξ and Verloop's constant B_1 as the physico-chemical parameters of the 4-substituted derivatives the following equation as one of the best ones was obtained:

$$\ln A\ (2.\ h) = 0.57\pi + 0.0107 \log \xi - 0.647\ B_1 + 0.619$$

$$r = 0.928 \qquad n = 7$$

unexplained share: 13.9 %

According to the equation, biological activity depends mainly on π. The contribution of ξ is only weak. ξ is a parameter being medial between hydrophobic and electronic parameters (9). The

contribution of B_1 in the equation can be regarded as to be almost constant since the B_1-values of CH_3, Br, Cl, CF_3, and CF_2CF_3 are all in the range of 1.52 - 1.98.

Using the Hansch Analysis with its classic parameters for the 19 potential fenamates, no significant correlation coefficients for the antiinflammatory activity at hour 4 could be obtained. The best equations for the antiinflammatory activity at hour 2 and 3, respectively, are the following ones:

$$\log A\ (2.\ h) = 0.214\ (\pm 0.135)\Sigma\pi - 0.375\ (\pm 0.299)\Sigma\sigma - 0.142\ (\pm 0.008)\Sigma E_s + 1.148\ (\pm 0.192)$$
$$r = 0.810 \quad s = 0.176 \quad \text{sign.} = 99.9\ \%$$

$$\log A\ (2.\ h) = 0.130\ (\pm 0.137)\Sigma\pi - 0.169\ (\pm 0.101)\Sigma E_s + 1.069\ (\pm 0.212)$$
$$r = 0.702 \quad s = 0.207 \quad \text{sign.} = 99.6\ \%$$

$$\log A\ (3.\ h) = 0.287\ (\pm 0.162)\Sigma\pi - 0.218\ (\pm 0.358)\Sigma\sigma - 0.112\ (\pm 0.105)\Sigma E_s + 1.077\ (\pm 0.230)$$
$$r = 0.763 \quad s = 0.211 \quad \text{sign.} = 99.6\ \%$$

$$\log A\ (3.\ h) = 0.238\ (\pm 0.143)\Sigma\pi - 0.214\ (\pm 0.105)\Sigma E_s + 1.032\ (\pm 0.221)$$
$$r = 0.733 \quad s = 0.215 \quad \text{sign.} = 99.8\ \%$$

$$\log A\ (\Sigma act.) = 0.224\ (\pm 0.135)\Sigma\pi - 0.199\ (\pm 0.298)\Sigma\sigma - 0.109\ (\pm 0.087)\Sigma E_s + 1.608\ (\pm 0.191)$$
$$r = 0.766 \quad s = 0.175 \quad \text{sign.} = 99.7\ \%$$

$$\log A\ (\Sigma act.) = 0.179\ (\pm 0.120)\Sigma\pi - 0.120\ (\pm 0.088)\Sigma E_s + 1.567\ (\pm 0.185)$$
$$r = 0.729 \quad s = 0.181 \quad \text{sign.} = 99.8\ \%$$

With regard to these equations, it has to be emphasized that the standard deviation of the coefficient of σ is rather high. It only exceeds the 90 % significance level in the first given equation. Therefore, σ should not be applied to the interpretation although the total significance of the equation is improved by it. Thus, the 2-parameter equations with $\Sigma\pi$ and ΣE_s should be preferred. Both the negative coefficient of π and the positive

coefficient of E_s indicate that more hydrophobic and voluminous substituents should improve activity. Surely, an optimum of hydrophobicity is to be expected although no significant quadratic term could be detected. The 2-methoxy group at the first aromatic ring proved to be without any influence on anti-inflammatory activity in these calculations. According to special repression calculations, no preferred position for substitutions at the second ring could be found.

The approach could certainly be improved by using ED_{50} values instead of values of percent inhibition at different times.

From the equations given above, the conclusion can be made that the antiinflammatory activity of the fenamates should be improved

- by trialkyl, trialkoxy or trihalogen substitution at the phenyl ring not bearing the COOH group; also tetra or penta substitutions could be of advantage,
- by di-(tri-, tetra-) substitution of longer alkyl or alkoxy moities.

This is in good agreement with the results obtained by Fig. 6 but represents also a certain extension of the results.

Thus, in comparison to Fig. 6, QSAR has not dramatically adduced new knowledge of a deeper and/or a more comprehensive insight into the present substance series concerning its optimization. Surely, this is partly or even mainly due to the fact that the substance series did not particularly fit well with the QSAR analysis used because derivation refers to a few substituents at several positions of the basic molecule. In that case, other methods have to be used which to a higher degree take into account the position of substitution.

However, with regard to the Free-Wilson Analysis, substituents are mostly determined by one equation only in the series of the

19 potential fenamate derivatives. In that case, calculations must be expected to merely give statistically non-significant and, therefore, trivial results. Thus, no respective calculations were performed.

The results obtained by QSAR are compatible with the above-mentioned receptor concept according to which the carboxyl group of the acidic NSA binds with an anionic binding site and a hydrophobic/lipophilic molecule moiety binds with an adjoining area or on the edge of the receptor being here dependent on the lipophilicity of the substituents and, therefore, of the compound. The question of an uniquely existing optimum fine-structure of the fenamates as well as of the capability of chelate complex formation with the heme iron of the cyclo-oxygenase complex cannot be answered by our results.

Summary

First, it is shown that it is not yet possible to outline a generally valid receptor model for the non-steroidal anti-inflammatory agents. This is demonstrated by three examples of receptor models, namely by the model according to Shen, by the receptor concept of Appleton and Brown, and by the concept concerning chelate complex formation between NSA and heme iron of the cyclooxygenase complex according to Peterson et al. This means that the "custom-made" synthesis of NSA with, perhaps, quantitatively and qualitatively better properties is not yet possible.

On the basis of this statement, QSAR investigations may be justified in order to optimize known NSA. In this paper, QSAR calculations on 21 fenamate derivatives are reported. For this, both the multivariate and the univariate Hansch Analysis were used. Altogether, 16 approaches to QSAR has been performed using 1 - 4 biological and 3 - 19 physico-chemical parameters,

respectively, with 7 - 21 objects. In all cases a dominating influence of π has been indicated. Other physico-chemical parameters seemed to be of less importance, e. g., σ, E_s, log ξ MR, MV, parachor, and Verloop's steric constants. Possible new fenamate structures of higher biological activity are briefly discussed.

References

(1) Shen, T. Y., in: Non-steroidal Anti-inflammatory Drugs (Garattini, S., and M. N. G. Dukes, eds.). Excerpta Med. Found., New York, 1965, p. 13

(2) Sallmann, A., in: Polyarthritiden (Wagenhäuser, F. J., Hrsg.). Verlag Hans Huber, Bern-Stuttgart-Wien, 1977, p. 295

(3) Gund, P., and T. Y. Shen. J. Med. Chem. 20, 1146 (1977)

(4) Shen, T. Y., in: Prostaglandins and Inflammation (Rainsford, K. D., and A. W. Ford-Hutchinson, eds.). Agents and Actions Suppl. 6 (1979) p. 177

(5) Appleton, R. A., and K. Brown, in: Arachidonic Acid Metabolism in Inflammation and Thrombosis (Brune, K., and M. Baggiolini, eds.). Agents and Actions Suppl. 4 (1979) p. 188

(6) Peterson, D. A., J. M. Gerrard, G. H. R. Rao and J. G. White, Prostaglandins and Medicine 2, 97 (1979)

(7) Peterson, D. A., J. M. Gerrard, G. H. R. Rao, E. L. Mills and J. G. White, in: Adv. in Prostaglandin and Thromboxane Res. (Samuelsson, B., P. W. Ramwell and R. Paoletti, eds.), Vol. 6 (1980) p. 157

(8) Paintz, M., H. Bekemeier, J. Metzner and U. Wenzel, in: Problems and Results in General Pharmacology (Bekemeier, H., and R. Hirschelmann, eds.). Martin-Luther-Universität Halle-Wittenberg, Wiss. Beitr. 1979/59 (R 57), p. 126

(9) Mazer, P. P., M. Paintz und U. Wenzel, Pharmazie 34, 174 (1979)

(10) Mager, P. P., U. Wenzel, R. Hirschelmann, J. Metzner, R. Böhm and E. Krause, in: 100 Years of the Salicylic Acid as an Antirheumatic Drug (Bekemeier, H., ed.). Martin-Luther-Universität Halle-Wittenberg, Wiss. Beitr. 1977/42 (R 34), p. 191

(11) Paintz, M., H. Bekemeier, J. Metzner, L. Reppel and U. Wenzel, this volume, p. 47

(12) Langner, A., V. Hagen, D. Lebes, and E. Krause, this volume, p. 35

(13) Hannig, E., und R. Brummer, Pharmazie 26, 135 (1971)

(14) Hannig, E., und E. Becke, Pharmazie 30, 289 (1975)

(15) Büge, A., personal communication

(16) Mager, P. P., Arzneimittel-Forsch. 25, 1006, 1270, 1355, 1475, 1745 und 1864 (1975)

(17) Mager, P. P., in: Drug Design (Ariëns, E. J., ed.) 9, 187 (1980)

(18) Egan, R. W., et al., J. Biol. Chem. 256, 7352 (1981)

(19) Hayaishi, O., in: Oxygen Free Radicals and Tissue Damage. Ciba Found. Symp. 65 (new series). Excerpta Med., Amsterdam-Oxford-New York, 1979, p. 141 – 142